and "activity", collectively, at least 23 times. Harris says right in the abstract "p53 is functionally ***inactivated*** by structural mutations, interaction with viral products, and endogenous cellular mechanisms in the majority of human cancers." (emphasis added). There is apparently no confusion by Harris as to what "inactivated" means and Harris is clearly a person skilled in the art. It does not seem appropriate that the Examiner should second guess the clearly skilled person in the art and imply that Harris doesn't know the meaning of the words he uses. Harris et al's concerns with mode of activation don't apply to p53as as presently claimed since the claimed p53as is always active due to the absence of the regulatory domain present in p53. **There is clearly no ambiguity in the use of the word "active" in the claims.**

The present invention is not difficult to understand in view of the specification and claims. One skilled in the art already knows a myriad of effects of p53. One skilled in the art already knows that p53 has growth regulating properties discussed in literally hundreds of documents. One skilled in the art already knows that p53 has a terminal negative regulatory domain that can turn off many, if not all, of the growth regulating properties of p53 under certain conditions. One skilled in the art already knows that when the negative regulatory domain is removed, the growth regulating properties of p53 can no longer be turned off.

The Examiner is referred to the references cited in the information disclosure statement as examples of such known information and is especially referred to Hupp et al cited by the Applicant that shows that removal of the C-terminal regulatory domain

permanently activates p53. ***This paper was accepted for publication in the prestigious technical journal "Cell" in 1992 after peer review. Neither the reviewers nor the magazine had any difficulty understanding the meaning of "active" p53 or the its" function".*** **It is again asserted that since those skilled in the art understand the meaning of these terms, any objection by the Examiner to their use should be dropped**.

Claims 16 and 19 have been rejected under 35 U.S.C. 112 as being indefinite because there is no definition "what constitutes a portion." With due respect to the Examiner, there are only 18 amino acids in the peptide in question. It is a relatively simple matter to truncate the peptide from either or both ends and test the truncated peptide to determine whether it raises an antibody response. With only 18 starting amino acids, there would seem to be no more than about ten possibilities for a "portion" that will raise an antibody response. Again, the Examiner seems to be making the invention more complicated than it really is. The "portion" would be expected to be linear since large amounts of folding could hardly be expected with 17 amino acids or less and in any case if the truncated sequence did naturally fold, the mode of operation need not be claimed or even described so long as an antibody response occurs. The inventors should not be required to restrict their invention to exclude reasonable modifications that are well within the purview of the skilled artisan. These claims are not indefinite.

Claims 1, 3-6, 8-11, 17 and 18 have been rejected under 35 U.S.C. 112 as containing subject matter not sufficiently described in the specification. This rejection should be withdrawn.

The Examiner should again be reminded that a patent specification is not intended to be a textbook including all information known and readily available to a skilled person. If such were not the case, every patent specification would be thousands of pages long rehashing known material ad nausem and hiding the nature of the improvement of the invention within unnecessarily included information.

The Examiner is making the invention much more complicated than it is. The invention is easy to understand and can be practiced to the extent of the breadth of the claims by one of even meager skill in the art in view of the teachings of the specification.

As previously discussed, one skilled in the art already knows a myriad of effects of p53. One skilled in the art already knows that p53 has growth regulating properties discussed in literally hundreds of documents. One skilled in the art already knows that p53 has a terminal negative regulatory domain that can turn off many, if not all, of the growth regulating properties of p53 under certain conditions. One skilled in the art already knows that when the negative regulatory domain is removed, the growth regulating properties of p53 can no longer be turned off.

The Examiner is again referred to the references cited in the information disclosure statement as examples of such known information and is especially referred to Hupp et al

cited by the Applicant that shows that removal of the C-terminal regulatory domain permanently activates p53.

The present invention points out that in view of the above, one would further expect that the growth regulating properties of p53 also could no longer be turned off if the terminal regulatory domain of p53 were modified or substituted to interfere with its function and demonstrated that to be the case by the discovery of terminally modified p53 that cannot be turned off (p53as) and that has a terminal sequence that raises a unique antibody.

One skilled in the art knows the sequence of p53. One skilled in the art knows many epitopes that can raise unique antibodies. One skilled in the art already knows how to truncate p53 to remove the negative regulatory domain and one skilled in the art already knows how to connect different sequences. **Attaching unique epitopes to proteins and peptides is now an essentially cookbook procedure performed routinely by laboratory technicians , e.g. in ELISA analysis and for the purpose of tags.**

Therefore, in view of the above discovery by the inventor of terminally modified p53 that cannot be turned off (p53as) having a terminal sequence that raises a unique antibody, the inventor concluded that p53 could be easily truncated to remove the negative regulatory domain and a large number of different terminal sequences could be substituted that raise unique antibodies. Once the inventor made this previously unobvious suggestion, anybody skilled in the art could practice the invention. The probability that such a new terminal sequence would also have a negative regulatory

domain effect upon p53 is infinitesimal. In view of her discovery and teaching it becomes clear that known methodologies may be combined to practice the invention and that it would be surprising if the p53as having unique terminal sequences did not function as active p53 and it would be further surprising if the p53as having unique terminal sequences did not raise the expected unique antibodies.

Further, if there are any p53 terminal sequences, as above described, that do not function as active p53 and that do not produce unique antibody, such could easily be detected in view of existing knowledge.

The Examiner states that the "specification does not contemplate the addition of exogenous, non-p53, sequences, such as his-tag epitopes." The Examiner's statement is not correct. For example, page 3, line 6 of the specification says, "To obtain a p53as the terminal amino acids of p53 are preferably modified, i.e. there is at least some substitution, as opposed to simple truncation." **This statement in no way restricts the substitution to p53 sequences.**

Page 2, last paragraph of the specification says "It is to be understood that p53as may be of natural or **synthetic** form, provided that, at a minimum, **terminal amino acids differ** from the 50 terminal amino acids of p53 so that the modified products will act the same as active p53 protein and is functionally equivalent to mouse p53as protein" (emphasis added). **This statement clearly contemplates non-p53 sequences at the terminal end.**

The Examiner apparently continues to be moved by the fact that usually substitution within a protein sequence to obtain similar function is complex. ***The Examiner would normally be correct but is not correct here.*** The functional sequence in p53 and p53as have been identified, are the same and are not being changed. ***Only the terminal regulatory domain is being affected by the changes to obtain the claimed p53as***. The total elimination of the regulatory domain in the known art while retaining p53 activity is dispositive of whether or not function may be retained while modifying that domain.

The teaching in the specification with respect to the specific p53as is clearly an example of terminally modified p53 having a unique epitope. The teaching is not limiting but an example.

It is thus clearly taught in the specification that modification of the terminal amino acids of p53 can be used to eliminate the regulatory domain. Nothing further is required to enable one skilled in the art to do it. The advantages of a unique C terminus epitope are also clearly taught. Again, at the present state of the art, any genetic engineering lab technician could add such a unique epitope to the C terminus.

A patent application is not supposed to be a textbook in well understood procedures. The teachings have been made of how to eliminate the negative regulatory domain of p53 by removing or altering the carboxy terminal sequence. Once this teaching is made, one of even menial skill in the art can do it. Further, the desirability of incorporating a unique epitope is taught in the specification. Again, once this teaching is

made, one of even menial skill in the art can do it. It is the concepts, taught in the present application, of eliminating the negative regulatory domain and incorporating a unique epitope which is at the heart of the invention. Once these concepts are taught, one having only minimal skill can practice them since only well known standard procedures are needed. Certainly no undue experimentation is required or necessary and the claims to the invention should not be unfairly restricted to merely a single example of the many possibilities for addition of unique epitopes.

In view of the above and other teachings in the specification, one skilled in the art would clearly know that other epitopes could be substituted in the C terminus. The claims have thus been appropriately limited to the minimum difference between p53 and p53as defined on page 2, last paragraph without addition of new matter.

The rejection should be withdrawn.

Claims 16 and 19 have been rejected under 35 U.S.C. 112 on the ground that use of "any portion of SEQ ID NO:1" is not enabled. As previously discussed, SEQ ID NO:1 is a short sequence and anybody with even minimal skill in the art would be enabled to easily determine whether a portion of that sequence raised an antibody. Undue experimentation would not be required as the test is practically "cookbook". The rejection should be withdrawn.

Claims 1, 3-5, 8-11, 17 and 18 have been rejected under 35 U.S.C. 102(b) as being anticipated by Wolf et al or Arai et al.

Claim 6 has been rejected under 35 U.S.C. 103 over Wolf et al and Arai et al above in view of Lee et al.

The claims have been amended to recite that the p53as is functionally equivalent to active wildtype p53. The mutant M-8 or p53as of Wolf et al or Arai et al. do not meet that requirement and do not suggest that requirement. The rejections have thus been overcome in a manner substantially equivalent to that suggested by the Examiner.

This amendment was not made earlier since until the statements by the Examiner in the present action concerning the distinguishing features of wildtype p53, the Examiner's position and need for the amendment was not appreciated. The amendment is necessary since it offers clarification of an intended distinguishing feature over the cited art.

Prior responses have already pointed out significant differences between this cited art and the claimed invention, on the basis that the term p53 was used to indicate p53 that can be activated to have normal activity, not mutants thereof that do not have and can not have normal p53 activity. The Examiner was apparently intending that the term p53 applied to mutant as well as non mutant forms. The amendment makes clear that p53as of the invention is intended to have the same activity as active normal (wildtype) p53.

M-8 in the cited art has the cyst residue of p53 at amino acid 132 replaced by a phe residue. A corresponding RNA or cDNA must have corresponding nucleic acid changes. M-8 further has a large 96 base pair ***embedded (not terminal)*** nucleic acid chain (and corresponding predicted amino acid) insert at nucleic acid 1092. These are not changes in

the terminal sequence but internal changes that apparently completely alter the function and nature of the protein as previously described. Some of the glaring differences in function between the mutant form and wildtype p53 are given in the prior responses.

In any case, the incorporation of the equivalency of function to wildtype p53 should be dispositive of this rejection since the cited references do not suggest functionality equivalent to active wildtype p53.

Any rejection relying upon M-8, or other mutant forms having abnormal function, against p53as is thus improper under both 35 U.S.C. 102 and 103. All rejections, based upon Wolf et al. or Arai et al or their combination with other cited art, should therefore be withdrawn.

The Examiner has again rejected claims 1, 3, 4, and 17 under 35 U.S.C. 103 over Han et al in view of Sambrook et al. and again it is asserted that the rejection is improper and should be withdrawn.

Han et al is interested in sequencing p53as cDNA and for that purpose only incorporates a p53as cDNA segment into a plasmid. The incorporated segment is only about one-third of a complete p53as cDNA. A whole p53as cDNA is never incorporated into a plasmid and in fact would be counterproductive for Han et al's purposes. Large DNA fragments are difficult and sometimes impossible to sequence thus Han et al actually teaches against incorporating an entire p53as cDNA sequence. Han et al. is interested in sequencing and, except for sequencing, teaches nothing at al concerning the study of function (activity) of either p53 or p53as. The "study" referred to by Han et al.

clearly relates to sequencing. There is no suggestion concerning methods for study of function except for sequencing by inserting a sequence into a plasmid. For the purposes of Han et al. it would have been counterproductive to include a complete p53as into a vector of any kind since long structures are difficult to sequence and are usually broken into smaller segments for that purpose.

Han et al does not incorporate p53as cDNA or any other functional p53 or p53as into anything.

In the present official action, the Examiner has acknowledged that Han et al does not incorporate p53as into anything but based entirely upon hindsight asserts that because Han et al inserts a p53as segment for sequencing it would be obvious to insert the whole p53as for purposes of function. The Examiner reaches that conclusion just because Han et al says "more precise biochemical and biological characterizations of AS-p53 protein ... appear to be critical in future studies of p53 function...." Attributing the teaching of incorporation of a complete p53as into a plasmid or virus based upon the above quoted statement Han et al. is impermissible hindsight at a minimum because Han et al. gives no reason whatsoever to expect that incorporation of a whole p53as into a plasmid or virus would somehow further the study of function. **The only reason that Han et al. incorporated a p53as segment was for sequencing not function. There is simply no suggestion that incorporation of such a segment might be useful to evaluation function and there is certainly no suggestion that incorporation of a whole p53as could somehow be useful for such a purpose.**

The position of the Examiner is contrary to the teaching of Han et al which is to sequence the segment. In general it is not desirable to try to sequence large segments; thus, following the teachings of Han et al there is no reason to incorporate the entire p53as. The Examiner's extension of Han et al to the entire p53as is classical hindsight. In the absence of the teaching of the present application, there would simply be no reason to incorporate the entire p53as into a vector of any kind.

Combining Han et al with Sambrook et al accomplishes nothing. It is a giant reach to state that because Sambrook et al generically discloses expressing large amounts of protein with nothing at all suggested concerning p53as, Han et al somehow suggests incorporating a whole p53as. This is a cleanly impermissible hindsight combination. Further, a generic teaching of expressing a large amount of protein is not equivalent to saying that long sequences can or should be incorporated into plasmids. Large amounts of protein and long sequences are not the same thing or even similar. One has essentially nothing to do with the other.

The rejection of Claims 5, 6, 8-11 and 18 over Han et al in view of Lee et al is a similarly flawed hindsight combination.

Han et al does not teach or suggest incorporation of p53as into anything, as previously discussed. Citation of Lee et al. which discloses nothing at all concerning p53as, does not cure this defect. The addition of Lee et al to the other cited references accomplishes nothing. Lee et al is generic and says nothing concerning p53 or p53as.

Neither reference suggests incorporating p53as into anything; therefore their combination certainly makes no such suggestion.

The rejection should be withdrawn.

In summary, none of the references cited by the Examiner in any of the rejections suggest incorporating p53as into anything. None of the cited references cure this critical defect in any of the other references.

All rejections should be withdrawn and all claims should be allowed which action is courteously requested.

Respectfully submitted,

Dated: April 27, 2000

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